Sustainability from the Beginning

How Statistical Thinking Can Bring Chemical Research into the Environmental Age

Since the urgent crisis of global warming took center stage in the public eye, chemical manufacturing processes have borne substantial blame. This argument holds water: for instance, the Haber-Bosch process — which produces ammonia and supports the food needs of half the world's population — contributes a full 1.4% to yearly carbon emissions and eats up 1% of global annual energy.

There is clearly a need for reform in chemistry, and the space to do so. Additionally, the chemical production sector is already the third-largest emitter of CO_2 in the world, with its impact expected to further swell over the next decade. But often flying under the radar in climate conversations is the research taking place at benches in industry and academia. Environmental reform can come at massive scale, certainly. But beginning at the benchtop is much more practical for setting a precedent.

Sustainability in the chemistry lab must be a set of actions, not just an idea, and beginning with a sustainable end in mind could prove transformative in the fight against climate change. This action-centric paradigm is increasingly prevalent at industry conferences, such as the JMP Discovery Summit Europe in Manchester, UK. The idea that statistics can address urgent sustainability concerns at the lab bench was central to presentations from groups including Moderna, Boehringer Ingelheim, and ORF Genetics.

This work will explore the metrics by which chemists can make their experiments greener, then move towards academic and industrial examples of green chemistry, before finally discussing how statistical methods and computational chemistry can lead chemical formulation and synthesis towards environmental friendliness.

Approaching Green Science in the 21st Century

The twelve criteria for green chemistry were described by American chemists Paul Anastas and John Warner in 1998. Some suggestions they laid out were obvious: minimizing waste, choosing friendlier solvents, and opting for reagents with renewable feedstocks (such as ethanol, produced from corn). However, some of their tips for greener science were more nuanced: maximizing the percentage of atoms in the reactants which remain present in the products (known as atom economy), minimizing the use of protecting and blocking groups, which add steps to synthetic paths, and maintaining materials efficiency in purification workups.

Anastas and Warner's criteria earned substantial acclaim, and the green chemistry approach has now been deployed in nearly every subdiscipline of the field, from analytical separations to organometallic synthesis. And, in 2015, the United Nations included the need for green chemistry in their list of 17 goals for a more sustainable future.

Advancements in chemistry which utilize these principals represent some of the most cutting-edge science currently taking place, and we need look no further than the 2022 Nobel Prize in chemistry for an example. Carolyn R. Bertozzi, Morten Meldal, and K. Barry Sharpless shared the 2022 award for their work in click chemistry, bcrafting a set of reactions which occur at room temperature, in air, and with 100% atomic efficiency. Studying reactions such as this one can help lay the groundwork for highly efficient and practical reactions in industry, and many leading research groups are pursing environmentally focused chemistry.

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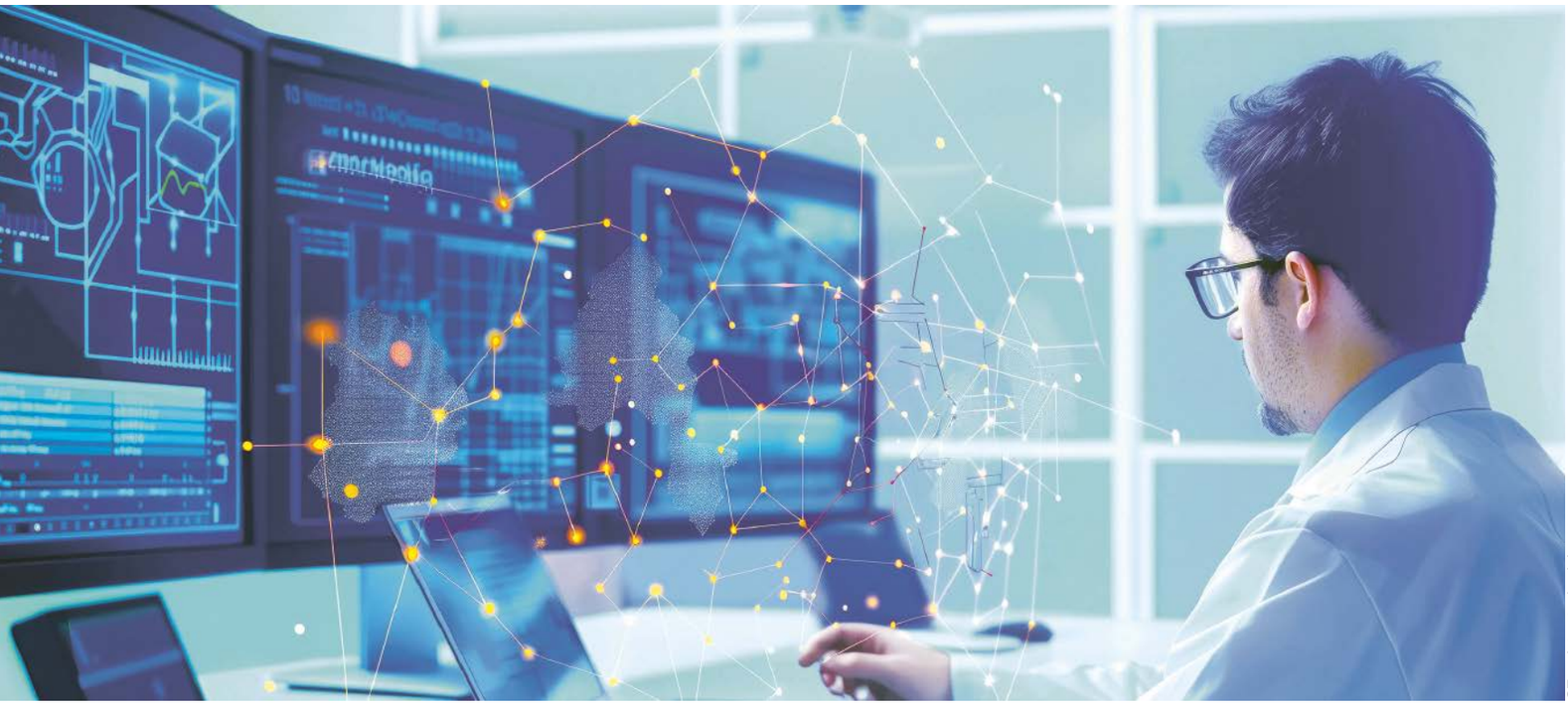
The Emergence of Green Chemistry at Scale

Chemists can and should optimize their benchtop operations for sustainability: each raindrop contributes to the flood, and each scientist can help in the fight against climate change. But the large-scale operation and mission of a com-



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pany also ought to be geared for environmentalism.

One such example is Icelandic plant biotechnology company and recombinant protein pioneer ORF Genetics. Their synthetic route to growth factors involves harnessing nature, not imitating it. Ásta María Einarsdóttir, research associate at ORF, notes that by using barley, they can create growth factors "on a very sustainable scale." Barley

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is recognized as a safe food substance and unlike many other growth factor production systems, it is endotoxin free. By using barley as a vessel to produce and store recombinant proteins, ORF Genetics can proceed without many of the hazards present in other growth factor synthesis schemes. Their work is an excellent example of beginning with a sustainable end in mind: barley seeds can be used not only as ideal production environments, but storage basins as well. Working towards an environmental goal and using clean methods to get there sets the stage for success in green chemistry.

But chemists don't need to be alone in their work towards more sustainable reactions. This is not only the age of the environment, but also the computational age of data processing. The construction of digital reaction networks allows to bypass what Weber et al. describe as the "extract-make-use-dispose" scheme and move towards renewable feedstocks.

There needs to be a bridge between sustainable chemistry at the benchtop and meaningful change at industry scale, and digital chemistry could provide the link. Julia O'Neill, founder of Direxa Consulting and former distinguished fellow at Moderna, says that "statistical methods and Design of Experiments (DOE) are essential to accelerating progress, especially products that are really needed." Specifically, O'Neill says that employing statistical methods can improve timescales not just for R&D but also for scale-up, manufacture, and commercialization. Moreover, methods such as DOE can help build product data libraries and allow for quicker translational work, like Moderna did to iterate its Spikevax Covid-19 vaccine in response to emerging variants of the virus.

A New, Statistical Era of Formulation and Synthesis

Statistically designed experiments are perfectly suited to the formulation realm, where multiple variables must be considered to produce an ideal product. One thing that O'Neill acknowledges is that there is natural hesitance about including statistics in this setting. "I think some of the perception that Design of Experiments can slow work down is just people thinking that there's an artificial impact to follow search," she says. Because while "some level of base training [in DOE] is essential," O'Neill continues, software like JMP "allows the experimenter to block out the nuisance sources of variation, get results in an all-in-one kind of study, and get a clear picture of cause and effect by the end." The power of a statistically designed experiment to simultaneously test several variables allows for deeper understanding of more variables, all with fewer materials and less time invested.

Consumer products manufacturers have seen this win-win paradigm and realized statistical thinking's potential in formulation. Now, companies such as Procter & Gamble are using statistical methods like DOE to usher in a new era of formulation, allowing for more complex mixtures and preparations than ever before. Old procedures and ways of thinking cannot push towards new sustainability goals, and embracing a digital-first mindset will facilitate cleaner exploration and development, right from the start.

"The potential of statistical thinking in chemical synthesis is starting to be recognized."

DOE has long had utility in chemical formulation and production, and for good reason. But the potential of statistical thinking in chemical synthesis is also starting to be recognized. Ignacio Aliagas et al. warn that the impact of drug development must be considered, responsible for hundreds of thousands of kilograms of waste through the benchtop and clinical phases. This is where DOE can help again: the technique can be used to measure multiple variable impacts in formulation schemes, but it can also be used to predict the efficacy of molecules for therapeutic use. This slims the pool of drug candidates, and, coupled with computationally-optimized synthetic routes, can provide a twofold environmental advantage. As Einarsdóttir continues, "being able to use statistics allows you to solve much more complex problems than you could before," opening near-limitless medical research possibilities.

One place where this kind of research takes place is the University of Miami Miller School of Medicine, where researchers use machine learning and modeling to predict potential drug scaffolds for cancer treatment, eliminating the need for wasteful trial-and-error syntheses in the laboratory. Then, these scaffolds are tuned via predictive modeling in silico to produce pre-clinical leads. Sarfaraz K. Niazi et al. note that this process, known as computer-aided drug design, can "result in drug synthesis processes that are both efficient and environmentally benign," providing an excellent example of beginning with a sustainable end in mind.

Conclusion

In Stephen Covey's world-renowned book 'The Seven Habits of Highly Effective People', habit number two is to begin with the end in mind. And for chemists to be effective in the environmental age, we must begin with the end in mind as well. From simply swapping a more toxic solvent for a tamer one, to changing the entire way that we produce growth factors and discover drugs, the thought processes behind sustainability in chemistry must run from beginning to end. Only by employing the principals of green chemistry at every step can chemists push back against climate change.

References to this article can be requested from the author.

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